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Clomipramine *vs* desipramine *vs* placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study

S. H. SINDRUP[1], L. F. GRAM[1], TINA SKJOLD[2], ELLEN GRODUM[3], K. BRØSEN[1] & H. BECK-NIELSEN[3]

Departments of [1]Clinical Pharmacology, Odense University, [2]Internal Medicine, Fredericia Hospital and [3]Endocrinology, Odense University Hospital, Odense, Denmark

1 The effect of clomipramine and desipramine on diabetic neuropathy symptoms was examined in a double-blind, randomised, placebo controlled, cross-over study for 2 + 2 + 2 weeks. Drug doses were adjusted according to the sparteine phenotype, i.e. extensive metabolisers were treated with 75 mg clomipramine day^{-1} and 200 mg desipramine day^{-1} whereas poor metabolisers were treated with 50 mg day^{-1} of both drugs. Nineteen patients completed the study.

2 Plasma concentration of clomipramine plus desmethylclomipramine was 70–510 nM in extensive metabolisers, *vs* 590 and 750 nM in two poor metabolisers. Desipramine levels were 130–910 nM, *vs* 860 and 880 nM.

3 Both clomipramine and desipramine significantly reduced the symptoms of neuropathy as measured by observer- and self rating in comparison with placebo. Clomipramine tended to be more efficacious than desipramine. Patients with a weak or absent response on clomipramine had lower plasma concentrations (clomipramine plus desmethylclomipramine < 200 nM) than patients with a better response. For desipramine a relationship between plasma concentration and effect was not established.

4 Side effect ratings did not differ for clomipramine and desipramine and on both drugs three patients withdrew due to side effects.

5 Compared with earlier results obtained with imipramine dosed on the basis of plasma level monitoring, clomipramine and desipramine on fixed doses appeared less efficacious whereas the side effect profiles were the same. At least for clomipramine, appropriate dose adjustment on the basis of plasma level monitoring may increase the efficacy.

Keywords clomipramine desipramine diabetic neuropathy

Introduction

Tricyclic antidepressants are widely used in the treatment of the symptoms of peripheral diabetic neuropathy. Imipramine (Kvinesdal *et al.*, 1984; Sindrup *et al.*, 1989, 1990a), amitriptyline (Max *et al.*, 1987) and nortriptyline (Gomez-Perez *et al.*, 1985) have in randomised, double-blind, cross-over trials been shown to be superior to placebo. For both imipramine (Kvinesdal *et al.*, 1984; Sindrup *et al.*, 1989, 1990a,b) and amitriptyline (Max *et al.*, 1987), a correlation between plasma drug concentration and effect has been established.

Tricyclic antidepressants are known to block α_1-adrenergic, H_1-histaminergic and muscarinic

Correspondence: Dr Søren H. Sindrup, Department of Clinical Pharmacology, Odense University, J. B. Winsløws Vej 19, DK-5000 Odense C, Denmark

cholinergic receptors, and presynaptic reuptake of 5-hydroxytryptamine (5-HT) and noradrenaline (Gram, 1983). Due to the existence of an endogenous pain suppressing system (Fields & Basbaum, 1984), dependent on opiates, 5-HT and noradrenaline, interest has focused on the monoamine reuptake inhibition as the mechanism of action of these drugs in this condition. In a recent study (Sindrup *et al.*, 1990a) we have shown that the selective 5-HT reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. By appropriate dosing according to plasma drug level monitoring, paroxetine may become as efficacious as imipramine (Sindrup *et al.*, 1990a). However, this does not exclude that interaction with noradrenergic receptor systems could be of importance and experimental studies have also indicated that certain antihistamines possess analgesic properties (Bjerring, 1990). Furthermore, it has been claimed that tricyclic antidepressants interact with rat brain opiate receptors at concentrations reached *in vivo* (Biegon & Samuel, 1979, 1980), although there is some controversy on this assumption (Hall & Ögren, 1981).

Obviously, the mechanism of action of tricyclic antidepressants in the treatment of diabetic neuropathy symptoms is not finally settled. Some of the classical TCA differ markedly in receptor profile, e.g. clomipramine acts predominantly as a 5-HT reuptake inhibitor (Hyttel, 1984), but its metabolite desmethylclomipramine inhibits the reuptake of both 5-HT and noradrenaline. In contrast, desipramine is a rather selective noradrenaline reuptake inhibitor without metabolites with effect on 5-HT reuptake (Gram, 1983). Clomipramine and to a less degree desipramine also block α_1-adrenergic, H_1-histaminergic and muscarinic cholinergic receptors (Gram, 1983). To examine the possible significance of these receptor differences we performed a randomised, double-blind, cross-over trial with clomipramine *vs* desipramine *vs* placebo.

Methods

Study design and medication

The study period comprised one week for baseline observations followed by a double-blind treatment for 2 + 2 + 2 weeks with clomipramine, desipramine and placebo in random order. The randomisation was carried out in blocks of six patients and drop-outs were substituted whenever possible. Drug doses were adjusted according to the sparteine phenotype as the metabolism of clomipramine (Balant-Gorgia *et al.*, 1986) and desipramine (Brøsen *et al.*, 1986) to some extent depend on the sparteine oxygenase. In extensive metabolisers (EM) of sparteine (metabolic ratio (MR) < 20) (Brøsen *et al.*, 1985), drug doses were clomipramine 75 mg day^{-1} and desipramine 200 mg day^{-1}, in poor metabolisers (PM) (MR > 20), it was 50 mg day^{-1} for both drugs. Clomipramine hydrochloride 25 mg (Anafranil®, CIBA-GEIGY), desipramine hydrochloride 25 mg (Pertofran®, CIBA-GEIGY) and placebo tablets were of identical size and colour. EM were given eight tablets (five additional placebo tablets in the clomipramine period) and PM were given two tablets in each of the three double-blind treatment periods as a single dose at 20.00 h. One patient (no 21, Table 1) was erroneously phenotyped as PM due to inhibition of the sparteine oxygenase by concomitant intake of dextropropoxyphene (Sanz *et al.*, 1989) before inclusion. Accordingly, this patient was treated with the PM doses of clomipramine and desipramine during the trial. Phenotyping was repeated after the trial and the patient was now classified as EM. The treatment periods were separated by at least 1 week for washout in EM, while the washout periods were extended to at least 3 weeks in PM, due to the very long elimination half-life of desipramine in this phenotype (Brøsen *et al.*, 1986). On the 13th and 14th day of each treatment period, blood for drug level measurements was collected at 08.00–09.00 h. Clomipramine, desmethylclomipramine and desipramine were assayed by quantitative thin layer chromatography (Gram *et al.*, 1983). The lower level of detection was 10 nM and the inter-assay coefficient of variation was 7–10%. All assays were run in duplicate.

Patients

Patients were recruited from two diabetic outpatient clinics and from general practitioners. They all had neurological signs of peripheral neuropathy and were troubled by several of the following symptoms: pain, paresthesia, dysesthesia, nightly exacerbation and sleep disturbances. The distribution of symptoms were typical for peripheral neuropathy. None had renal or cardiac dysfunction, a diagnosis of pernicious anaemia, reduced serum levels of vitamin B_{12} or folic acid, or untreated hypothyroidism.

Twenty-six patients were included. Six patients withdrew due to side effects; three during

Table 1 Patient characteristics at the time of inclusion in the study

Patient number	Sex	Age (years)	DM deb. age	Duration of neuropathy symptoms (years)	Neuropathy symptoms		Neurological signs[2]		
					Pain quality	Additional symptoms[1]	Reduced touch sensibility	Muscle weakness	Reflex loss
3	F	58	47	3	burning, aching	P, D, H	+	+	+
4	M	46	28	5	stinging	P	+	+	+
5	F	56	32	5	lance	P, D, H	+	−	−
6	F	55	44	8	throbbing	P	+	−	+
7	F	78	61	2	aching	P, D, H	+	−	+
8	M	40	23	10	lance, tenderness	P, D, H	+	+	+
9	M	55	39	4	aching, lance, tenderness	P, D, H	+	−	+
10	M	43	28	3	aching, lance, burning	P, D	+	−	−
12	F	62	44	1	aching, lance, burning	P, D, H	+	+	+
13	M	62	57	5	aching, lance, tenderness	P, D	+	−	+
14	F	42	27	3	lance	P	−	−	+
15	F	29	20	5	stinging, lance, cramps	P	+	+	−
18	M	44	25	2	aching, cramps	P, H	+	+	+
19	F	62	8	20	lance, cramps	H	+	+	+
21	M	55	30	5	aching, lance	P, D, H	+	+	+
23	F	43	39	1	aching, lance, tenderness	P, D	−	+	−
24	F	72	68	4	aching, stinging	P, H	+	+	+
25	M	64	44	3	lance, cramps, tenderness	P, H	+	+	+
26	M	73	41	2	aching, lance	P, D, H	−	−	+

[1] P: paresthesia, D: dysesthesia, H: hypesthesia.
[2] +: sign present, −: sign absent.

clomipramine (nausea, dizziness, tiredness, confusion) in the first active treatment period and three during desipramine (nausea, tiredness, dizziness) in the first (two patients) or second (one patient) active treatment period. One patient dropped out due to lack of pain relief after 1 day on clomipramine. Nineteen patients thus completed the study. Clinical data on these patients are given in Table 1. Three patients (nos 5, 10, 23) showed only minor neurological deficits, in two of these (nos 10 and 23) the diagnosis of peripheral neuropathy was confirmed by nerve conduction and EMG studies. In one patient (no 18) ankle/arm systolic blood pressure index was below 0.9 bilaterally and arterial insufficiency could thus partly be responsible for the symptoms. Sixteen patients were insulin treated, while three (nos 9, 23, 24) were treated with glibenclamide and/or metformin.

Effect recording and evaluation

At the end of each treatment period, the neuropathy symptoms were assessed by a physician (SHS or TS) using a 6-item neuropathy observer scale with items for pain, paresthesia, dysesthesia, numbness, nightly deterioration and sleep disturbances (Kvinesdal *et al.*, 1984; Sindrup *et al.*, 1989, 1990a). Symptoms were scored as not present (= 0), very mild (= 0.5), mild (= 1.0), moderate (= 1.5) or severe (= 2.0). During each treatment period, patients performed daily self ratings by use of the same neuropathy scale. One patient aged 78 years did not perform this rating in a consistent manner, and therefore self rating data on this patient were not included in the data analysis. In each patient the median of the neuropathy score during the last week of each treatment period was used for data analysis. The scoring on the 6-item neuropathy observer scale was carried out independently of the selfrating and served as the primary measure of effect. A Marstock stimulator (Somedic AB, Stockholm, Sweden) (Fruhstorfer *et al.*, 1976) was used to record heat pain threshold on the right wrist at the end of each treatment period.

At the end of each treatment period an observer rating of side effects including dry mouth, sweating, palpitations, visual disturbances, constipation, micturition difficulties, concentration trouble, fatigue, orthostatic dizziness, constant dizziness, nausea, headache, nervousness and tremor was used. Each item was assessed as not present (= 0), very mild (= 0.5), mild (= 1), moderate (= 1.5) or severe (= 2.0). The patients were thoroughly instructed only to report symptoms that started or worsened during each treatment period.

Statistical analyses were carried out by the Mann-Whitney test, the Kruskal-Wallis test, The Friedman test, the Page test, the Wilcoxon's test for pair differences, and Spearman rank correlation using the MEDSTAT program package version 2.1 (Wulff & Schlichting, 1988). An extension of the Friedman test was used for comparison of treatments against each other and against placebo (Siegel & Castellan, 1988).

The study was approved by the regional ethics committee, and patients consented to participate on the basis of verbal and written information.

Results

Table 2 lists treatment sequences, sparteine phenotypes, plasma drug concentrations, and the scores on the observer and self rating neuropathy scale during placebo, clomipramine and desipramine.

The dose correction in PM (clomipramine: factor 1.5, desipramine: factor 4) was not sufficient since the dose corrected steady state levels in PM were 2–10 (median 4) times higher than in EM during clomipramine and 4–20 (median 6) times higher during desipramine (Table 2).

Periodical effect was tested for all sequences placebo-clomipramine *vs* clomipramine-placebo, placebo-desipramine *vs* desipramine-placebo and clomipramine-desipramine *vs* desipramine-clomipramine for the neuropathy observer scale and no significant differences were found (P = 0.09–0.64, Mann-Whitney test). Furthermore, periodical effect was tested through placebo score minus mean of clomipramine and desipramine score in patients treated with placebo in the 1st *vs* placebo in the 2nd *vs* placebo in the 3rd period ($P > 0.10$, Friedman test). Likewise, residual effect was tested for all treatment combinations (Mann-Whitney test) and for all treatments together in the six treatments sequences (Kruskal-Wallis test) and no significant differences were found (P = 0.14–0.76), except for a residual effect from clomipramine indicated in the clomipramine-desipramine *vs* desipramine-clomipramine combination (P = 0.03, Mann-Whitney test). At the end of the placebo period (13th–14th day) neither clomipramine, desmethylclomipramine or desipramine could be traced in the patients' plasma. Total observer and self rating neuropathy scores during placebo were not signifi-

Table 2 Treatment sequence, sparteine phenotype, plasma drug concentrations, and symptom score

Patient number	*Treatment sequence*[1]	*Sparteine phenotype*[2]	*Plasma concentration (nM)*[1]		*Total observer/self rating score*[1]		
			CL + DCL	*DMI*	*PL*	*CL*	*DMI*
3	DMI → PL → CL	EM	—	750	3.0/4.0	8.0/8.0	3.0/3.5
4	PL → DMI → CL	EM	135	160	8.5/7.0	7.0/7.0	7.5/6.5
5	CL → PL → DMI	EM	250	560	8.0/4.5	0.0/0.0	0.5/0.5
6	CL → DMI → PL	EM	230	910	7.0/7.0	2.5/2.0	2.0/3.5
7	PL → DMI → CL	EM	120	540	11.5/—	7.0/—	7.0/—
8	CL → DMI → PL	EM	190	470	10.5/10.5	0.5/0.5	4.0/2.0
9	CL → PL → DMI	EM	290	285	8.0/6.0	3.5/3.5	2.0/2.5
10	DMI → CL → PL	EM	70	130	3.5/3.5	3.5/3.5	2.5/2.5
12	PL → CL → DMI	EM	420	820	9.5/7.5	2.0/0.0	6.5/3.0
13	CL → DMI → PL	EM	260	290	4.5/1.0	1.0/1.0	5.5/1.0
14	DMI → CL → PL	EM	370	910	9.5/8.5	6.5/7.0	8.5/6.5
15	PL → DMI → CL	EM	490	850	6.5/4.0	4.0/4.0	3.5/3.0
18	DMI → PL → CL	EM	185	530	4.0/5.0	4.5/4.0	7.5/7.0
19	DMI → CL → PL	PM	750	880	6.0/7.0	3.0/4.5	3.5/2.5
21	PL → DMI → CL	EM[3]	250	205	8.5/7.5	5.5/3.0	9.0/9.5
23	PL → CL → DMI	EM	470	500	6.0/2.5	0.0/0.0	5.5/5.0
24	DMI → PL → CL	EM	510	580	6.0/4.5	4.0/4.0	3.5/4.0
25	DMI → CL → PL	EM	470	720	5.5/6.0	4.0/5.0	7.5/7.5
26	CL → PL → DMI	PM	590	860	11.0/9.0	7.0/9.0	7.0/6.0
				Rank sum[4]	50.0/46.5	28.5/29.0	35.5/32.5

[1] PL: placebo, CL: clomipramine, DCL: desmethylclomipramine, DMI: desipramine.
[2] EM: extensive metabolisers (dose: clomipramine 75 mg day^{-1}; desipramine 200 mg day^{-1}). PM: poor metabolisers (dose: clomipramine 50 mg day^{-1}, desipramine 50 mg day^{-1}).
[3] Treated with PM doses of both clomipramine and desipramine (see text).
[4] Friedman test for observer rating, $P < 0.001$ (multiple comparisons, critical rank sum difference = 14.8 (α = 0.05) and 13.1 (α = 0.10)). Friedman test for self rating, $P < 0.005$ (multiple comparisons, critical rank sum difference = 14.4 (α = 0.05) and 12.8 (α = 0.10)).

cantly different from scores during the baseline period ($P = 0.22$ and $P = 0.27$, Wilcoxon's test).

The effect of treatment was tested by multiple comparisons based on a Friedman test (Table 2) (Siegel & Castellan, 1988). The score on both the observer and the self rating neuropathy scale showed significantly better effect (lower score) on clomipramine ($P < 0.05$) and desipramine ($0.05 < P < 0.10$) than on placebo, whereas there could not be detected any difference between clomipramine and desipramine score ($P > 0.30$). The median reduction in neuropathy observer score as compared with placebo was on clomipramine 39% (95% confidence limits 27–79%) and on desipramine 32% (0–46%).

The reduction in score in percent of the placebo score on neuropathy observer scale did not correlate with plasma drug concentration either in the clomipramine ($r_s = 0.19$, $P > 0.20$), or in the desipramine ($r_s = 0.20$, $P > 0.20$) treatment period. Patients with a weak or absent response on clomipramine appeared to have lower plasma levels of clomipramine plus desmethylclomipramine than patients with a marked response, whereas such a relationship was not present during desipramine treatment (Figure 1).

As shown in Table 3 clomipramine reduced scores of all items except hypesthesia, whereas on desipramine only the reduction in paresthesia score was statistically significant ($P < 0.05$), although the median scores of all items showed a reduced level compared with placebo. There were no differences between clomipramine and desipramine.

In patients that did self rating and responded (> 25% reduction in neuropathy score as compared with placebo score) on clomipramine ($n = 14$) and desipramine ($n = 10$) the onset of effect was immediate and appeared to be maximal within one week (Figure 2).

Heat pain thresholds did not change significantly during the study.

In the 19 patients that completed the study the total side effect score was significantly higher during clomipramine (median 4.0, rank sum = 42.0) and desipramine (median = 4.5, rank sum 46.5) than during placebo (median = 0.02, rank sum = 25.5) ($P < 0.05$, multiple comparison extension of the Friedman test), whereas there was no difference between clomipramine and desipramine ($P > 0.30$). The most common side effects were dry mouth, sweating, ortho-

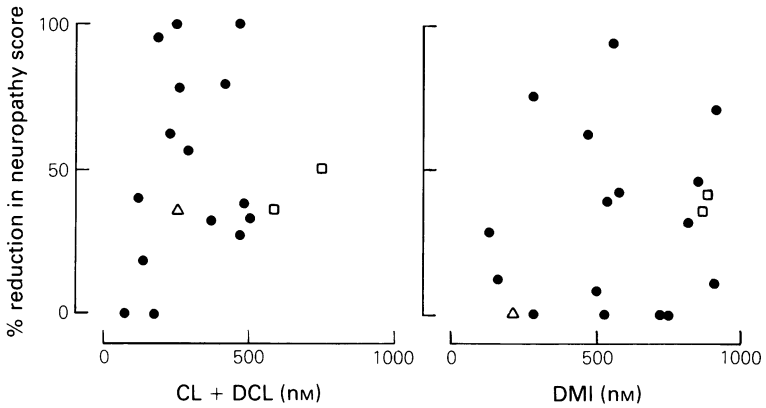

Figure 1 Effect given as percent reduction in neuropathy score in relation to the plasma concentration of clomipramine (CL) + desmethylclomipramine (DCL) (left) and desipramine (DMI) (right) in extensive metabolisers of sparteine (•), poor metabolisers of sparteine (□), and the extensive metaboliser erroneously treated with the poor metaboliser doses of clomipramine and desipramine (△).

Table 3 Median (range) of single items score on the neuropathy observer scale during placebo, clomipramine and desipramine

	Placebo	*Clomipramine*	*Desipramine*
Pain	1.5 (0.5–2.0)	0.99 (0–2.0)	1.02 (0–2.0) a
Paresthesia	1.49 (0–2.0)	0.99 (0–1.5)	0.99 (0–2.0) ab
Dysesthesia	0.99 (0–2.0)	0.02 (0–1.5)	0.46 (0–1.5) a
Hypesthesia	1.01 (0–2.0)	0.54 (0–2.0)	0.99 (0–2.0)
Nightly aggravation	1.49 (0–2.0)	0.51 (0–1.5)	0.99 (0–2.0) a
Sleep disturbance	1.04 (0–2.0)	0.47 (0–1.5)	0.96 (0–2.0) a

a: clomipramine significantly different from placebo ($P < 0.05$).
b: desipramine significantly different from placebo ($P < 0.05$).
For all other comparisons $P > 0.30$.
Statistical analysis by the multiple comparison extension of the Friedman test.

static dizziness and fatigue, but six patients reported of one or more of these symptoms during placebo.

Glycemic control was assessed at the end of baseline, placebo, clomipramine and desipramine periods. Neither postprandial blood glucose (median 13.6 *vs* 12.8 *vs* 14.5 mmol l^{-1}), fructosamine (3.18 *vs* 3.36 *vs* 3.22 mmol l^{-1}), or glycosylated haemoglobin (10.0 *vs* 9.9 *vs* 9.9%) showed any significant differences between placebo, clomipramine and desipramine (P = 0.21–0.95, Friedman test), or any systematic change from inclusion (baseline) and through the three double-blind treatment periods (P = 0.10–0.27, Page test).

Discussion

Several tricyclic antidepressants have been shown to relieve the symptoms of diabetic neuropathy in double-blind, placebo controlled trials (Gomez-Perez *et al.*, 1985; Kvinesdal *et al.*, 1984; Max *et al.*, 1987; Sindrup *et al.*, 1989). Clomipramine and desipramine have not previously been studied in this condition. In a double-blind study clomipramine was superior to acetylsalicylic acid in painful non-diabetic mononeuropathies (Langohr *et al.*, 1982) and in a recent study it was shown that desipramine relieves postherpetic neuralgia (Kishore-Kumar *et al.*, 1990). We found both compounds effective but clomipramine tended to be more efficacious than desipramine and patients with a weak or absent response on clomipramine appeared to have lower plasma levels and apparently optimal response on clomipramine may require plasma drug levels (clomipramine plus desmethylclomipramine) above 200 nM. No such relationship between plasma concentration and effect was apparent for desipramine.

The median reduction in neuropathy score

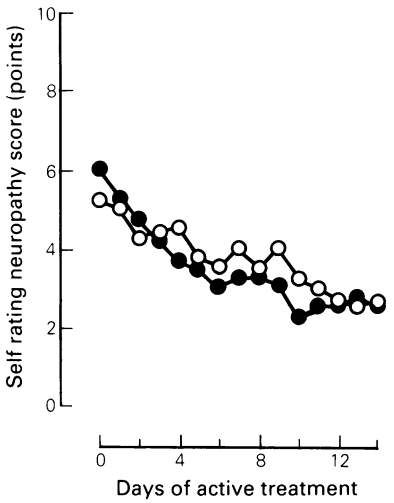

Figure 2 Median of daily self rating of neuropathy symptoms during active treatment periods following immediately after baseline/placebo period in patients responding to clomipramine (●——●, $n = 14$) and desipramine (○——○, $n = 10$).

as compared with placebo score was 39% on clomipramine and 32% on desipramine, whereas imipramine in optimal plasma level monitored doses showed a median 71% reduction in score (Sindrup *et al.*, 1990a). However, as indicated above, clomipramine may, as for imipramine (Kvinesdal *et al.*, 1984; Sindrup *et al.*, 1989, 1990b), prove to be more efficacious if the doses are adjusted according to the plasma levels. With imipramine the effective levels (imipramine plus desipramine) in treatment of diabetic neuropathy (Sindrup *et al.*, 1990b) are lower than the lower effective level (700 nM) required for antidepressive effect (Reisby *et al.*, 1977). In the same way the effective levels of clomipramine plus desmethylclomipramine indicated in this study are substantially lower than those indicated for the antidepressive effect of clomipramine (750 nM) (Danish University Antidepressant Group, 1986). An action of these drugs on neuropathy symptoms through their antidepressive properties, as suggested by Turkington (1980) is unlikely, both due to the fast onset of action (Figure 2, Sindrup *et al.*, 1990a) and the lower effective plasma levels required.

Dose adjustment according to sparteine phenotype has not previously been attempted. The dose reductions in PM were not fully sufficient, which could to some extent have been predicted for desipramine from the difference in single dose clearance between EM and PM (Brøsen *et al.*, 1986). EM doses of desipramine (200 mg day^{-1}) would have yielded clearly toxic drug levels (> 3000 nM) in PM.

In this study clomipramine and desipramine produced more side effects than placebo, but no differences could be detected between the two drugs and they caused the same number of withdrawals (three patients each) due to side effects. With respect to side effects none of these drugs appear to be superior to imipramine. The double-blind character of the study was not invalidated by the side effects, since clomipramine and desipramine appear to have similar side effect profile and 'side effects' were also frequently reported during placebo treatment ($n = 6$).

The mechanism of action of tricyclic antidepressants in pain treatment has been related to the endogenous pain suppressing system in CNS involving several transmitters; opiates, 5-HT and noradrenaline (Fields & Basbaum, 1984). While there has been most attention on the serotonergic mechanisms, there are experimental data that point to the involvement of noradrenaline (Hwang & Wilcox, 1987; Proudfit, 1988). Our previous study showing efficacy of a selective 5-HT reuptake inhibitor (Sindrup *et al.*, 1990a) and this study showing some effect from a relatively selective noradrenaline reuptake inhibitor (desipramine) indicate that both noradrenaline and 5-HT may be involved. It is suggested that the inhibitory effect of monoamines on nociception occurs in the spinal cord and at this level there is an intimate interaction between 5-HT and adrenergic neurons (Proudfit, 1988), therefore noradrenaline may exert an indirect effect on 5-HT synapses and *vice versa*. The tricyclic antidepressants investigated so far do all have post receptor blocking activity besides their monoamine reuptake properties. Therefore it still cannot be excluded that some of the effect of tricyclic antidepressants is mediated via a direct interaction with central opiate receptors (Biegon & Samuel, 1980), or through blockade of H_1-histaminergic receptors (Bjerring, 1990), or blockade of peripheral α_1-adrenergic receptors (Young & Clarke, 1985).

In conclusion, this study shows that both clomipramine and desipramine reduce the symptoms of peripheral diabetic neuropathy. Clomipramine tends to be more efficacious than desipramine and it is suggested that by appropriate dose adjustment the efficacy of clomipramine could be increased, while this may not be the case for desipramine. Compared with imipramine neither clomipramine nor desipramine seems to be preferable with regard to side effects.

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